Docket No. PRD2166USPCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Marc Karel Jozef Francois	Confirmation No: 1592
Serial No.	:	10/585,754	Art Unit: 1624
Filed	:	July 12, 2006	Examiner: Adam C. Milligan
For	:	MITRATAPIDE ORAL SOLUTION	

The Commissioner For Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Dear Sir:

This paper is in response to the Final Office Action mailed November 23, 2009. Applicants respectfully request a pre-appeal brief review of the above referenced application.

SUPPORTING ARGUMENTS ON REVIEW

Rejection of Claims 1, and 3-12 under 35 U.S.C. § 103(a)

The Examiner rejects Claims 1-12 under 35 U.S.C. 103(a) as being unpatentable over Heeres (WO96/13499 – See IDS dated 7/12/2006) in view of Chen (2002/0147201) and Basit et al. (The Effect of Polyehtylene Glycol 400 on Gastrointestinal Transit: Implications for the Formation of Poorly Water Soluble Drugs, Pharmaceutical Research, Volume 18, No. 8, 2001). The Examiner proffers that Chen teaches multiple oral formulations which may include various active ingredients (See pp. 26-27, examples 8-10). The Examiner further proffers that even parenteral compositions may be administered orally where the solution is aqueous and aqueous solutions are generally accepted as orally acceptable.

Heeres does not teach an oral solution

Applicants disagree with the new characterization of the Heeres reference and the instant invention. In the March 30, 2009 ("March 2009 Office Action"), the Examiner characterized the Heeres reference, *inter alia*, "teaches an oral solution comprising 1 mg/ml of mitratapide (page 17, compound no. 22), a solvent (page 26, example 8), and sucrose as a taste modifying agent (page 26, example 8)." (See page 4 of March 30, 2009)

In the current, November 23, 2009 Office Action ("Office Action"), the examiner characterizes the Heeres reference as disclosing "multiple oral formulations" which include the various active ingredients. Applicants note the difference between oral formulations and oral solutions. Particularly, while a capsule (Example 9 in Heeres) and/or tablet (Example 10 in Heeres) may be considered oral formulations, there is no support that either the capsule or tablet is considered an oral solution as claimed in the instant invention.

While Heeres does teach an oral solution comprising mitratapide and a solvent (page 26, example 8), it should be noted that said Example 8 on page 26 teaches an aqueous solution, not an oral solution. Further, the Office Action alleges even parenteral compositions maybe administered orally where the solution is aqueous and aqueous solutions are generally accepted as orally acceptable. However, the Applicants again point the Examiner to the text of Heerse. Particularly, the complete sentence starting on page 10, line 16, of Heeres reads "For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included." Again this sentence teaches that for aqueous solutions comprising mitratapide other ingredients may be added to aid solubility. The present invention is an oral solution, not an aqueous solution. Accordingly, the present invention cannot be obvious in view of Heeres in view of Chen and Basit et al.

Chen and Basit do not teach the addition of PEG 400 to an oral solution comprising mitratapide

In the March 2009 Office Action, the Examiner alleged, *inter alia*, Heeres and Basit taught the addition of PEG-400 to an oral solution comprising mitratapide. However, the Applicants point out that Basit discloses a study wherein ten healthy subjects were given either orange juice or orange juice with PEG-400. In addition, the patients were given non-disintegrating pellets encapsulated within a hard gelatin capsule. (See Basit page1146). The use of PEG-400 in orange juice and the separate administration of a hard gelatin capsule is not analogous to the instant invention.

In addition, Applicants respectfully disagree with the March 2009 Office Action regarding the aforementioned characterization of US-2002/0147201. First, the March 2009 Office Action states (bottom of page 4) "US-2002/0147201 teaches that one way to increase active agent solubility is to add plasticizer such as polyethylene glycol (PEG) to the composition (paragraph 64 of US-2002/0147201)." This is repeated on page 5 of the Office action in the second to last paragraph.

The Applicants point out, however, that §64 in US-2002/0147201 has to be read in conjunction with §58:

> § 58: "In addition to the active agent and glycyrrhizin that dosage forms may incorporate additional ingredients. These additional ingredients include, for example, preservatives, chelating agents, surfactants, taste modifiers, buffering agents, antacids, plasticizers, water soluble fillers, water insoluble fillers, binders, glidants, film formers, enteric coatings, solvents, coloring agents, thickening agents, osmotic agents, and semi-permeable membrane-forming agents."
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> §64: "Plasticizers include glycerin, sorbitol, propylene glycol, polyethylene glycol, triacetin, triethyl citrate (TEC), acetyl triethyl citrate (ATEC) and other citrate esters. Preferable, the dosage forms of the present invention can include 0 to 40% plasticizers on a weight basis."

- Nowhere in the paragraphs 58 and 64 is it mentioned that plasticizers in general, or polyethylene glycol in particular, are added in order to increase the solubility of the active ingredient. Plasticizers in general, or polyethylene glycol in particular, are cited as "additional ingredients" but their specific purpose is nowhere mentioned in US-2002/0147201. As defined in Wikipedia, "Plasticizers or dispersants are additives that increase the plasticity or fluidity of the material to which they are added ...". Accordingly, US-2002/0147201 does not teach the skilled person the incorporation of polyethylene glycol in order to increase the solubility.
- In addition, it should be noted that US-2002/0147201 in general teaches a means for increasing the solubility and bioavailability of active ingredients by forming a complex of said active ingredients with glycyrrhizin. (*See* e.g., paragraph 19 and 45.) Furthermore, US-2002/0147201 teaches that these complexes (from active ingredient and glycyrrhizin) are highly water-soluble. If the skilled person would have followed the teaching of US-2002/0147201, the artisan would have made complexes of mitratapide with glycyrrhizin. The present invention however does NOT make use of glycyrrhizin.

Furthermore, it should be stressed that the mitratapide solutions of the present invention are not aqueous solutions but use an organic solvent. In view of this point, Applicant's amended claim 1 to include the subject matter of claim 2, thereby providing further clarity of the organic solvents in claim 1.

In addition, if the skilled person would have started from the teaching of WO-96/13499 and would have combined it with the teaching of US-2002/0147201 then the skilled person would have ended up with an aqueous solution of mitratapide complexed with glycyrrhizin. As explained in paragraph 0008 of the present application due to the very limited solubility of mitratapide in water, the skilled person would not look into the development of aqueous solutions and would not combine the teaching of WO-96/13499 with US-2002/0147201. In the absence of the combined teaching of WO-96/13499 with US-2002/0147201, the Basit et al. reference stands on its own and there is no motivation to combine WO-96/13499 with the Basit et al. reference.

Heeres, Chen and Basit combined do not disclose a oral solution comprising mitratapide as recited in Claim 1

The teaching of WO-96/13499 is directed to aqueous solutions comprising mitratapide. The teaching of US-2002/0147201 is directed to a means for increasing the solubility and bioavailability of active ingredients by forming a complex of said active ingredients with glycyrrhizin. If the skilled person would have started from the teaching of WO-96/13499 and would have combined it with the teaching of US-2002/0147201 then the skilled person would have ended up with an aqueous solution of mitratapide complexed with glycyrrhizin. Since the present invention is a non-aqueous solutions of mitratapide in an organic solvent, this is very different than what would have been done by the skilled person when following the teaching of WO-96/13499 and US-2002/0147201. Further, there is no motivation to combine WO-96/13499 with the Basit et al. reference. Accordingly, the applicants respectfully submit that the claimed compounds are not prima facie obvious over WO96/13499 in view of United States Patent Publication 2002/0147201 and Basit et al. Thus, applicants request withdrawal of the rejection under 35 U.S.C. §103(a) and respectfully request reconsiderations and allowance of claims 1, 3-12.

Respectfully submitted,

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